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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER

PRIEBE, SCOTT DAVID

ART UNIT PAPER NUMBER

1632

DATE MAILED: 03 10 2003

3

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.
10/077,894

Applicant(s)
Bartlett et al.

Examiner
Scott D. Priebe, Ph.D.

Art Unit
1632



-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☐ Responsive to communication(s) filed on _____.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-20 is/are pending in the application.
- 4a) Of the above, claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1-20 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☒ The drawing(s) filed on Feb 20, 2002 is/are a) ☒ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- 11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.
If approved, corrected drawings are required in reply to this Office action.
- 12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

- 13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
a) ☐ All b) ☐ Some* c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
*See the attached detailed Office action for a list of the certified copies not received.
- 14) ☒ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).
a) ☐ The translation of the foreign language provisional application has been received.
- 15) ☒ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

- 1) ☒ Notice of References Cited (PTO-892) 4) ☐ Interview Summary (PTO-413) Paper No(s).
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948) 5) ☐ Notice of Informal Patent Application (PTO-152)
- 3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s). 6) ☐ Other:

Art Unit: 1632

DETAILED ACTION

Priority

Applicant has not complied with one or more conditions for receiving the benefit of an earlier filing date under 35 U.S.C. 119(e) as follows:

The second application (which is called a continuing application) must be an application for a patent for an invention which is also disclosed in the first application (the parent or provisional application); the disclosure of the invention in the parent application and in the continuing application must be sufficient to comply with the requirements of the first paragraph of 35 U.S.C. 112. See *In re Ahlbrecht*, 168 USPQ 293 (CCPA 1971).

The instant claims are directed generically to compositions and methods for using chimeraplasty to correct mutations in a dystrophin gene, in particular, or any gene, in general, in any animal. Provisional application 60/135,139, filed 5/21/99 does not describe or support the claimed compositions or methods as they are generically claimed. The provisional application describes only correcting the GRMD mutation in dogs and prophetically treating human muscular dystrophy, where delivery of the chimeraplast with FUGENE 6 is required. The provisional application does not mention, even in passing, treating any other animals or not delivering the chimeraplast without the use of FUGENE 6. The subject matter instantly claimed is fully described in provisional application 60/174,388, and the effective filing date for the instant claims is 1/3/00.

Art Unit: 1632

Specification

The disclosure is objected to because of the following informalities. The current status of all US non-provisional applications cited in the specification should be updated, e.g. --now abandoned-- or --now US Pat. No. ...--. See page 1, line 6; page 2, line 32; page 3, lines 3 and 11, for example.

Appropriate correction is required.

The disclosure is objected to because it contains embedded hyperlink and/or other form of browser-executable code. Applicant is required to delete all embedded hyperlinks and/or other forms of browser-executable code. See MPEP § 608.01.

The use of numerous trademarks has been noted in this application, e.g. FUGENE 6, LIPOFECTAMINE, *inter alia*. Trademarks should be capitalized wherever they appear **and** be accompanied by the generic terminology. The specification does not disclose the generic terminology for these compounds.

Although the use of trademarks is permissible in patent applications, the proprietary nature of the marks should be respected and every effort made to prevent their use in any manner which might adversely affect their validity as trademarks.

Art Unit: 1632

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-20 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Claims 1-4 are directed to a composition limited to correcting a mutated dystrophin gene in muscle cells *in vivo*, where the mutation can be any type of mutation, i.e. claims are not limited to point mutations. Claims 5-12 are directed to using such a composition to correct a mutated dystrophin gene in muscle cells *in vivo*. Claims 13-20 are directed to using such a generic composition (not limited to correction of dystrophin mutations) to correct a mutation of any type in any cells *in vivo*. The two main areas where the specification fails to provide an enabling disclosure are how to make effective oligonucleobases commensurate in scope with the claims, and how to use the claimed *in vivo* method for the asserted specific and substantial utility. The specification does not disclose any specific and substantial utility for the composition or methods other than the treatment of genetic disorders in general, and muscular dystrophy in particular. There is no guidance in the specification for using the claimed invention for any purpose other than treatment of genetic disease. The specification fails to provide an enabling

Art Unit: 1632

disclosure for treating any disease in general, or muscular dystrophy in particular. There is no evidence of a well-established utility for merely correcting mutations in a few cells *in vivo* that do not lead to some "real world" benefit, such as treatment of a genetic disease.

The invention is directed to an emerging technology, chimeraplasty, that employs chimeric oligonucleotides of a very specific structure to correct or introduce point mutations in DNA. So far, conversion of only single nucleotide mutations has been observed. The oligonucleobases used in this technology are also known in the art as chimeraplasts, correction mutational vectors (CMV), and chimeric RNA/DNA oligonucleotides (RDO). This technology is as yet in its infancy and highly unpredictable with respect to the structure of the oligonucleobases that are effective; the cell and tissue types that are amenable to such correction; and the mode of delivery *in vivo* with respect to the route of administration and the inclusion of ancillary compounds to facilitate delivery, e.g. targeting ligands, and uptake, e.g. lipids, of the oligonucleobase. To date, most applications of chimeraplasty have been limited to correcting mutations in cultured cells. A few *in vivo* applications of chimeraplasty have been described, primarily in liver. The mechanism of action is unknown, but is expected to involve DNA repair and recombination.

Many laboratories have been unsuccessful in getting this method to work even *in vitro*, and where it has been successful the efficiency has been highly variable. Only a few laboratories have succeeded with this technology, and it is unclear to the others what the key to success is (see Strauss, Nature Med. 4 (3): 274-275, 1998; Stephenson, JAMA 281 (2): 119-121, 1999; Smaglik,

Art Unit: 1632

The Scientist 14 (1): 13, 2000; van der Steege et al., Nature Biotech. 19 (4): 305-306, 2001). In Smaglik, Steer is quoted as saying: "If you don't get a boatload of this material into cells, the kinetics just doesn't favor the reaction", and he estimates that uptake of from 1000 to 10000 copies per cell may be required. Yoon (Biogenic Amines 15 (1): 137-167, 1999) discloses that the cell type may be important, particularly with respect to levels of DNA repair and recombination activities in different cells, and cell cycle, cell metabolism and transfection conditions. In one application, the efficiency of correction in highly transformed cells, e.g. HeLa cells, was high, whereas no correction was observed in primary or immortalized human keratinocytes. In another application, 30 repeated experiments resulted in a conversion frequency ranging from 0.01% to 15%. See Yoon, pages 151, 153 and 157-159). Stephenson discloses that this technology "faces many technical challenges before it is clear whether the method can move from bench to bedside." Smaglik compares chimeraplasty to a word processor's search-and-replace function, and states "before it can be "shipped" to the clinic, its developers and others must optimize and debug it." Potentially the major hurdle is developing methods to deliver the chimeraplasts to appropriate cells and tissues. The success of at least one *in vivo* application depended greatly upon the particular delivery vehicle used (See Stephenson, and Smaglik in comments attributed to Steer).

With respect to the structure of the oligonucleobase, it is unclear what structures of oligonucleobase are embraced by the claims (see rejection under 35 USC 112, 2nd para.). The specification provides a generic structure for an oligonucleobase, shown in Figure 1, that is

Art Unit: 1632

formed from a single strand comprises regions of deoxyribonucleotides (DNA) and ribonucleotides (RNA). The single strand contains regions that pair to form a fully paired duplex, either RNA/DNA duplex or DNA/DNA duplex. One strand of the duplex region is DNA, while the other is either all RNA or a RNA-DNA-RNA chimeric sequence. The duplex region is divided into three segments, two flanking regions (RNA/DNA) and a core mutator region (RNA/DNA or DNA/DNA) which contains the mutation to be put into the desired target DNA sequence. The duplex region is identical to the target DNA sequence except for the point mutation that is to be introduced into the target DNA sequence. All of the working examples involve oligonucleobases that have the structure shown in Figure 1; this structure is the same as that in the prior art.

Ye et al. (Mol. Med. Today 4 (10): 431-437, 1998) and Yoon disclose that this general structure for chimeraplasts was arrived at empirically after several rounds of failures, and Yoon warns that "the key parameters of the structure of RDO have yet to be determined for an efficient gene conversion", i.e. success for deviation from this generic structure is unpredictable. The RNA/DNA duplex was used to take advantage of the natural recombinogenicity of RNA/DNA hybrids, and DNA/DNA hybrids either do not work or are very inefficient. The hairpin capped ends were included to avoid destabilization or destruction of the RDO by cellular helicases or exonucleases. For correction of mammalian genes, it was necessary to link the RNA/DNA duplex by a double hairpin (comprised of dT residues) and to use a GC clamp to anchor one of the hairpins in order to protect the 5'- and 3'-ends of the RDO from exonucleolytic cleavage, and

Art Unit: 1632

to prevent tandem ligation of RDOs. To date, the only nucleotides used in constructing the RDOs have been natural deoxyribonucleotides and either natural ribonucleotides or 2'-O-methyl-ribonucleotides. 2'-O-methyl-ribonucleotides were used so that the RDO would be resistant to RNase H, and would not affect the stability of an RNA/DNA duplex compared to natural RNA. Yoon stresses that different modified ribonucleotides would have to be tested, as their effect on mammalian recombination or repair activity is unknown. [See Ye et al., page 433; and Yoon, page 138 (bottom), 141, 143 (bottom) through 144, page 163].

The prior art of record and the instant specification only shows chimeraplasts for correction of single nucleotide point mutations. Stephenson discloses that only small corrections, 1-3 consecutive nucleotides, may be corrected (page 120, col. 2). Smaglik, in comments attributed to co-inventor Rando, discloses that this upper limit of 3 nucleotides is theoretical, and that most researchers have only attempted correcting single nucleotides. Yoon (page 160) discloses "that 2 mismatches "may be sufficient to disable gene conversion" in chimeraplasty. The instant specification discloses that when the chimeraplast could potentially correct two nucleotides, correction of only one nucleotide was observed.

The prior art does not disclose covalently attaching a targeting ligand, e.g. for muscle cells directly to the chimeraplast, as suggested by claims 4, 10 and 18. Although the prior art does disclose attaching hepatocyte-specific ligands to carrier molecules used to deliver the chimeraplast. There is no evidence of record as to whether modification of the oligonucleobase by covalent attachment of a ligand would interfere with the correction process. It is well known

Art Unit: 1632

in the field of DNA repair that proteins and other adducts on DNA are preferentially removed, which would suggest that the presence of the ligand on the oligonucleobase may target its strands for destruction by the DNA repair system, raising doubts as to the operability of this embodiment.

The instant specification discloses no advances over the prior art in designing chimeraplasts. It provides no more guidance on the design and composition of chimeraplasts than can be found in the prior art (particularly speculative disclosures found in patents and patent applications). The specification merely provides a listing of various modifications of the basic structure, but provides no evidence or guidance as to the operability of any of them. In light of the prior art, this disclosure amounts simply to an invitation to excessive experimentation in designing new types of chimeraplasts.

With respect to treating specific genetic diseases, the specification lists several potential diseases that might be treatable, but provides specific guidance and working examples only for muscular dystrophy in mice and dogs. Treatment of muscular dystrophy in humans is clearly contemplated and embraced by the claims. In Smaglik, co-inventor Rando is quoted as saying that "Most [MD] in humans does not involve point mutations". However, the specification fails to identify a single known mutation in the human dystrophin gene that would be amenable to the method claimed.

The working examples in the specification demonstrate correction of a dystrophin mutation in a few cells *in vivo* using mouse and dog model systems. However, the efficiency of

Art Unit: 1632

correction was very low, and was limited to nuclei within 1-2 mm of the injection site. To achieve even this minimal result in the dog, the lipid carrier FUGENE 6 was essential for delivery of the oligonucleobase. Naked oligonucleobases did not work in the dog, although they did work in mice. Some expression of a protein that appeared to be corrected dystrophin was observed in both the mouse and dog. No quantitation of protein expression was determined in the dog, however, in the mouse only 10-20% of transfected fibers along the needle track expressed the protein. However, no evidence of a meaningful phenotypic change, such as an amelioration of muscular dystrophy symptoms, was observed in either mouse or dog.

The low level of correction and protein expression observed raises serious doubts as to the potential efficacy of using the claimed method for treating muscular dystrophy. Feero et al. (Gene Therapy 4: 664-674, 1997) noted that to treat Duchenne muscular dystrophy by gene therapy would require "restoration of about 20% of normal dystrophin levels in affected muscles," where the muscles in humans represent 30% of total mass. Pegoraro et al. (Neurol. 45: 677-690, 1995) studied asymptomatic and symptomatic female carriers of Duchenne muscular dystrophy. Symptomatic carriers had a skewed pattern of preferential inactivation of the normal X chromosome. In carriers, the muscle fibers undergo a process of degeneration of dystrophin-negative fibers followed by a regeneration of fibers, in some of which the mutant X chromosome is inactivated. Over time, this leads to an increase in dystrophin-positive fibers at the genetic level, i.e. an increase in fibers where the normal X chromosome is active. In symptomatic carriers, however, while this process leads to an increase in myonuclei that are genetically

Art Unit: 1632

dystrophin-positive, 65% of the genetically dystrophin-positive myonuclei do not produce detectable levels of dystrophin protein. The fibers are essentially dystrophin-negative, even though active copies of a normal dystrophin gene is present. This would suggest that correction of a mutant dystrophin gene by the claimed method would also generally fail to lead to production of active dystrophin.

The disclosed experiments on the mouse have been published in Rando et al. (PNAS 97(10): 5363-5368, 2000). In discussing the therapeutic potential of this method for treatment of muscular dystrophy the authors stated that such application "requires both theoretical and technical considerations". The percentage of DMD patients having point mutations is unknown, but estimated to be less than 20%. Most DMD patients have large deletions not amenable to treatment by chimeraplasty. In discussing the challenges that would have to be overcome before the method would be a viable treatment, the authors, which include co-inventor Rando, stated:

Technically, the challenges are more *daunting*. First, the low efficacy of gene conversion would have to be *substantially* improved, potentially involving methods to facilitate chimeraplast uptake into muscle cells, enhance the transport of chimeraplasts to the nucleus, and enhance the efficiency of chimeraplast-mediated gene "repair." Second, as with viral-mediated gene therapy, a possible immune response against the "novel protein" [normal dystrophin] would be a consideration, and an effective method of delivery of the vector to a tissue as massive and distributed as skeletal muscle would have to be developed. Clearly, *major advances* in systemic delivery will be necessary. *(emphasis added)*

In Smaglik, co-inventor Rando in describing using chimeraplasty to treat muscular dystrophy had indicated the "efficiency is *very* low" (emphasis added), and that the animal model experiment did not mean that a treatment for MD in humans is on the horizon. Smaglik observes that treating

Art Unit: 1632

large areas of muscles, rather than targeting a local area as in the animal model experiment, "could be very difficult" because muscle, unlike liver, does not have a series of blood vessels leading directly to a specific region.

Given the very low efficiency of gene correction observed in the instant working examples, and the extensive research and development that would be required to overcome the hurdles recognized in the art before this method could be used in treatment of muscular dystrophy, and the lack of guidance in the specification for overcoming these hurdles, one skilled in the art would clearly be required to engage in excessive and undue experimentation in order to practice the invention for treatment. Absent any evidence for any other well established or readily apparent utility for the claimed invention, the claimed invention is not enabled.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-20 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1, 5 and 13 each recite the structure of an "oligonucleobase". The description of this structure is vague and unclear. The claims do not clearly convey what structures are

Art Unit: 1632

embraced by the claims. It is unclear for example, how the recited structure relates to the generic structure shown in Figure 1. The specification describes oligonucleobases which at a minimum for a fully paired duplex containing a "mutation" to be introduced into the target DNA flanked by sequences identical to the target DNA. The claims does not recite any duplex structure or complementary sequence that could form a duplex structure. It is unclear what the "heterologous region" is heterologous to, to the homologous regions or to the target sequence. Also, in claims 1 and 13, there is no nexus between either the oligonucleobase or the first and second fragments of the mutated gene and the mutation to be corrected. There is no recited element in the oligonucleobase which is required for performing the recited function of correction. Claim 5 suffers from a similar defect. The first and second homologous regions are homologous to first and second fragments, respectively, which flank a mutation. It is unclear whether the oligonucleobase comprises any region corresponding to the mutation, for example.

Claim 5 recites the limitation "the dystrophin gene" in line 1. There is insufficient antecedent basis for this limitation in the claim. Presumably a subject has at least 2 dystrophin genes in every single cell of its body; or in the case of skeletal muscle cells, which are multinucleate, every single nucleus of every cell.

Claim 5 recites the limitation "the point mutation" in line 9. There is insufficient antecedent basis for this limitation in the claim.

Claims 3, 7, and 15 contain the trademark/trade name FUGENE™ 6. Where a trademark or trade name is used in a claim as a limitation to identify or describe a particular material or

Art Unit: 1632

product, the claim does not comply with the requirements of 35 U.S.C. 112, second paragraph. See *Ex parte Simpson*, 218 USPQ 1020 (Bd. App. 1982). The claim scope is uncertain since the trademark or trade name cannot be used properly to identify any particular material or product. A trademark or trade name is used to identify a source of goods, and not the goods themselves. Thus, a trademark or trade name does not identify or describe the goods associated with the trademark or trade name. In the present case, the trademark/trade name is used to identify/describe an undisclosed lipid compound and, accordingly, the identification/description is indefinite.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless --

(a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1, 5, 8, 9, 11, 13, 16, 17, and 19 are rejected under 35 U.S.C. 102(a)&(b) as being clearly anticipated by Bartlett et al. (Nature Biotech. Short Rep. 9:163-164, 1998).

Bartlett et al. describes correcting the mouse *mdx* mutation *in vivo* by intramuscular injection of a chimeric oligonucleotide comprising RNA and DNA that comprises a duplex

Art Unit: 1632

complementary to the region including the *mdx* mutation , except for the desired substitutions that were incorporated.

Claims 1, 5, 8, 9, 11, 13, 16, 17, and 19 are rejected under 35 U.S.C. 102(a) as being clearly anticipated by Rando (Neurol. 52 (Suppl. 6): A374-A375, April 1999).

Rando describes correcting the mouse *mdx* mutation *in vivo* by intramuscular injection of a chimeric oligonucleotide, MDX1, comprising RNA and DNA that comprises a duplex complementary to the region including the *mdx* mutation , except for the desired substitution that was incorporated.

Claims 13, 14, and 19 are rejected under 35 U.S.C. 102(b) as being clearly anticipated by Steer et al., WO 98/49350.

Steer et al. discloses correcting a mutation in the rat *UGT1A1* gene *in vivo* by injection of a chimeric oligonucleotide, MDX1, comprising RNA and DNA that comprises a duplex complementary to the region including the mutation , except for the desired substitution that was incorporated. The oligonucleotide was complexed with a lipid.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

Art Unit: 1632

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103© and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1, 2, 5, 6, 13 and 14 are rejected under 35 U.S.C. 103(a) as being unpatentable over either Bartlett et al. or Rando as applied to claims 1, 5, 8, 9, 11, 13, 16, 17, and 19 above, and further in view of Feero et al. (Gene Therapy 4: 664-674, 1997).

Bartlett et al. and Rando have been described above. Neither reference discloses complexing the oligonucleotide with a lipid.

However, Feero et al. discloses compositions and methods for delivery of polynucleotides to muscle by complexing the polynucleotide with a liposomal vector to which is attached transferrin, a muscle cell specific ligand to improve the specificity and efficiency of transfection of muscle cells, ultimately for delivery to DMD muscle cells. Feero et al. showed that regenerating myotubes of DMD patients have elevated levels of transferrin receptor.

Art Unit: 1632

Therefore, it would have been obvious to one of skill in the art at the time the invention was made to have complexed the oligonucleotides of either Bartlett et al. or Rando into liposomes of Feero et al. in order to improve the specificity and efficiency of transfection of muscle cells *in vivo*, particularly for dystrophin-negative cells which have elevated levels of transferrin receptor.

Conclusion

The art made of record and not relied upon is considered pertinent to applicant's disclosure. Taubes (Science 298: 2116-2120, 2002) provides a recent summation of the state of the art of chimeraplasty. The consensus opinion of the most experienced artisans in the area of gene repair and gene therapy is that chimeraplasty using the type of oligonucleotides described in the instant specification simply does not work (see page 2120, from para. bridging col. 1-2 through col. 2). This publication reinforces the grounds of rejection set forth above.

This is a continuation of applicant's earlier Application No. 09/576,081. All claims are drawn to the same invention claimed in the earlier application and could have been finally rejected on the grounds and art of record in the next Office action if they had been entered in the earlier application. Accordingly, **THIS ACTION IS MADE FINAL** even though it is a first action in this case. See MPEP § 706.07(b). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

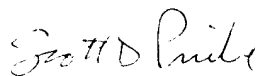
Art Unit: 1632

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no, however, event will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Certain papers related to this application may be submitted to Art Unit 1632 by facsimile transmission. The FAX numbers are (703) 308-4242 or (703) 305-3014 for any type of communication. In addition, FAX numbers for a computer server system using RightFAX are also available for communications before final rejection, (703) 872-9306, and for communications after final rejection, (703) 872-9307, which will generate a return receipt. The faxing of such papers must conform with the notices published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993) (see 37 CFR 1.6(d)). NOTE: If applicant *does* submit a paper by FAX, the original copy should be retained by applicant or applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED, so as to avoid the processing of duplicate papers in the Office.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Scott D. Priebe whose telephone number is (703) 308-7310. The examiner can normally be reached on Monday through Friday from 8 AM to 4 PM. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Deborah Reynolds, can be reached on (703) 305-4051.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.



SCOTT D. PRIEBE, PH.D.
PRIMARY EXAMINER